REMARKS

Applicant thanks the Examiner for participating in an interview with Applicant's representative on December 17, 2003, in which the Examiner and Applicant's representative discussed the patentability of the pending claims in view of the cited references. In particular, the patentability of a vaccine composition in view of Macek *et al.* (U.S. 5,853,715) and Studdert (U.S. 5,084,271) was discussed. No agreement was reached.

Supplemental Response to Claim Rejections Under 35 U.S.C. § 103

In the outstanding Office Action, mailed July 30, 2003, the Examiner rejected claims 1-6, 8, 10, 12-15, 17-22, 27, 28, 32-35, 37, 39, 41-45, 48, and 49 as being unpatentable over Macek *et al.* (U.S. 5,853,715), Studdert (U.S. 5,084,271), and Lund (U.S. 3,920,811), as further evidenced by O'Callaghan (U.S. 5,795,578), and in further view of Brown *et al.* (U.S. 4,500,513), Letchworth, III *et al.* (U.S. 5,462,734) and Kit *et al.* (U.S. 5,292,693). Applicant traverses the rejection for the reasons as noted in the Amendment Under 37 C.F.R. § 1.111, filed on October 30, 2003, and further for the following reasons.

As previously noted, the KyA strain of the EHV-1 virus is attenuated and has been shown to be avirulent in young horses. (*See* Matsumura *et al.*, *Vet. Micro.* 48 (1996) 353-365). DNA analyses of the genome of EHV-1 KyA have identified deletions that remove or alter genes corresponding to ORF 1, ORF 2, gI, gE, 10k ORF, ORF 63, ORF 17, and EUS4. (*See* Colle III *et al.*, *Virus Res.* 43(1996) 111-124, at 121). Colle III *et al.* indicates that the absence of membrane glycoproteins gE and gI may be of particular importance in reducing the virulence of EHV-1 KyA. (*See id.*) The

Matsumura *et al.* and Colle III *et al.* references were previously submitted in an information disclosure statement filed on August 3, 2001, however, Applicant has included complimentary copies herewith for the Examiner's convenience.

Applicant respectfully contends that one skilled in the art would not be motivated to use inactivated EHV-1 KyA as a vaccine against EHV-1 and/or EHV-4, and that it is unexpected that a composition including chemically inactivated EHV-1 KyA would be an effective vaccine against EHV-1 and/or EHV-4.

Applicant's arguments are supported by the findings of Matsumura *et al.* regarding a study based on administering live EHV-1 KyA to horses. Matsumara *et al.* inoculated six foals intranasally with live EHV-1 KyA. (*See id.* at 354-55.) As reported by Matsumara *et al.*, "[a]fter the KyA inoculation, antibody response against EHV-1 was weak or undetectable in six horses." (*See id.* at 363. (emphasis added).) Further, Matsumara *et al.* state that the "low antibody response and reduced virus replication observed in horses inoculated with the KyA strain might be explained to some extent by the lack of gE and gI genes in the KyA genome." (*See id.* (emphasis added).) Therefore, as disclosed by Matsumara *et al.*, live EHV-1 KyA did not generate a strong neutralizing antibody response to EHV-1 (*i.e.*, a strong humoral response). Because the generation of a strong humoral response is generally accepted as a necessary characteristic of an effective inactivated vaccine, Matsumura *et al.* teach away from the use of an inactivated EHV-1 KyA vaccine to protect horses against EHV-1 and/or EHV-4.

After inoculating the foals with live EHV-1 KyA, Matsumara *et al.* then challenged the foals with a virulent strain of EHV-1, strain 89c25, again by inoculating the foals intranasally. Matsumara *et al.* observed that the foals immunized with strain 89c25 showed antibody responses. (*See id.* at 360.) While Matsumara *et al.* noted

that attenuated KyA may induce "EHV-1 specific cellular immunity," as evidenced by "the protective results observed in the KyA inoculated horses after the challenge [with virulent strain 89c25]," (see id. at 363), it is generally accepted that effective cell-mediated immunity typically requires viral replication. As such, one skilled in the art would not be motivated to use chemically inactivated KyA as a vaccine against EHV-1 and/or EHV-4.

Applicant's argument is also supported by the findings of Zhang *et al.*, *Virus* Research **56** (1998) 11-24 ("Zhang"), which was submitted with the information disclosure statement filed on August 3, 2001. A complementary copy is provided herewith for the Examiner's convenience.

Applicant respectfully contends that the results of Zhang demonstrate there was no reasonable expectation of success that a composition including chemically inactivated KyA would be an effective vaccine against EHV-1 and/or EHV-4. Zhang investigated protective immunity against EHV-1 infection in mice, as induced by administering a recombinant EHV-1 gD fusion protein (*i.e.*, gD fused to glutathione-S-transferase, ("GST-gD")). Zhang *et al.* examined mice immunized subcutaneously or intranasally with GST-gD, GST (as a control), heat-killed KyA (as a control), or medium (as a control), and then challenged with virulent EHV-1 strain RacL11. (*See id.* at 17-19, and Figure 4.) As such, Zhang *et al.* disclose subcutaneous and intranasal administration of heat-killed KyA to mice. Zhang *et al.* observed equivocal results, however, in regard to immunity induced by the heat-killed KyA. For example, to analyze immunity to EHV-1 infection, Zhang *et al.* monitored the immunized mice for weight loss over a period of eight (8) days. (*See id.* at 19, Figure 4.) In these weight loss monitoring experiments, mice immunized intranasally with heat-killed KyA performed no better than mice immunized intranasally with GST, (see id. at Figure

4.B.). Mice immunized subcutaneously with heat-killed KyA performed similarly to mice immunized subcutaneously with GST-gD or GST, based on body weight, and better than mice simply inoculated with medium, (see id. at Figure 4.A.). Emphasizing the importance of the results observed for intranasal administration, Zhang *et al.* note that "[b]ecause EHV-1 infection initiates as a respiratory infection, it was important to ascertain whether GST-gD [or other vaccines] delivered directly to the upper respiratory tract was protective." (*See id.* at 18.)

Zhang *et al.* also studied the degree of protection in immunized mice by challenging the mice with RacL11 and then testing for the presence of the virus in the lungs of the challenged mice. (*See id.* at 20 and Table 2.) Mice immunized subcutaneously with GST-gD and heat-killed KyA demonstrated similar results. (*See id.*) Zhang characterized the levels of protection elicited by the GST-gD and heat-killed KyA as low in comparison to the protection resulting from infection with the live attenuated KyA virus. In discussing their results, Zhang *et al.* state that "regardless of the synthetic or recombinant gD immunogen used, the subsequent protection against challenge with pathogenic RacL11 was not as complete as that elicited by prior infection with nonpathogenic KyA (citing Colle III *et al.*, 1996, and Table 2)." (*See id.* at 21 (emphasis added).)

In emphasizing the importance of cell-mediated immunity for effective EHV-1 immunization, Zhang *et al.* concluded that "these data suggest that activation of both humoral and cellular compartments of the EHV-1-specific response may be required if effective, long-term protection is expected." (*See id.* at 21 (emphasis added).) In particular, Zhang *et al.* note that "[a] role for CD8 T cells in controlling EHV-1 infection has been implied from both equine and murine studies," and "[t]he low levels of protection elicited by the gD subunit vaccines compared to EHV-1 KyA infection may

reflect the absence of a virus-specific CD8 T cell response generated by these non-replicating antigens." (*See id.* (emphasis added).) Because CD8 T cell activation generally requires expression of viral antigens on the surface of infected cells, effective CD8 T cell activation typically requires viral replication. As such, it is respectfully submitted that one skilled in the art would not be motivated to use chemically inactivated KyA as a vaccine against EHV-1 and/or EHV-4 based on the teachings of Zhang *et al.*

In summary, Applicant respectfully contends that a *prima facie* case of obviousness is not established by the cited references. Moreover, based on the combined teachings of Matsumura *et al.*, Colle III *et al.*, and Zhang *et al.* and the other references cited in the Office Action dated July 30, 2003, there was no reasonable expectation of success that a composition including chemically inactivated KyA would be an effective vaccine against EHV-1 and/or EHV-4. For the foregoing reasons and as stated in the Amendment Under 37 C.F.R. § 1.111, filed on October 30, 2003, Applicant respectfully requests reconsideration of the rejection under 35 U.S.C. § 103.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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